REMARKS

The Final Office Action of May 10, 2005, has been received and reviewed. This paper is submitted under 37 CFR § 1.114 in response to the Final Office Action of May 10, 2005. It is accompanied by a Request for Continued Examination. Claims 1-7, 10-16, 18 and 19 were pending in the application. All pending claims stand rejected. Applicants are amending claims 1, 13, and 14. Claims 8, 9, and 17 were previously canceled. Applicants are also canceling claims 10, 18 and 19, and to add claims 20 and 21 at this time. No new matter has been added. All amendments and claim cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested in light of the recent Examiner interview, as well as the amendments and remarks presented herein.

Personal interview of June 21, 2005

Applicants would first like to thank the Examiner for the courtesy extended during the interview of June 21, 2005. As recorded in the Examiner's Interview Summary: "Discussed claim amendments to distinguish over art reference. Proposed amendments will be discussed at a later time. Kit claims as currently worded would remain rejected." Applicants believe that the Examiner's Interview Summary adequately presents the substance of the interview. MPEP § 713.04. If further comments are deemed necessary, the Office is kindly requested to contact the applicant's undersigned representative.

Rejections under 35 U.S.C. § 102(b)

Claims 1-5, 10-13, and 15 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Grathwohl *et al.* (*Journal of Virological Methods*, 64:205-216, 1997). Claim 10 has been canceled and its content has been incorporated into claim 1 thus obviating the need to respond directly to the claim 10 rejection. All of the other claims rejected under 35 U.S.C. § 102(b) are dependent on claim 1. Claim 1 discloses obtaining a sample from a mammal and using that sample to prepare a test set and a control set that are then assayed for the presence of prion protein. Treatment with guanidine thiocyanate or a functional equivalent thereof is then used to denature proteins in the test set, while the control set is left untreated. Guanidine

thiocyanate denaturation enhances antibody reactivity towards the prion form of PrP ("PrP^{sc}"), while antibody reactivity towards the normal form of PrP ("PrP^{c}") is reduced or unchanged. In this test, a relative signal increase following guanidine thiocyanate denaturation is objective proof of the presence of PrP^{sc}. Applicants propose that, for at least the following five reasons, Grathwohl *et al.* does not anticipate the rejected claims.

First, samples in the instant case are prepared for analysis in a way that is fundamentally different than the procedure taught by Grathwohl *et al.* In brief, Grathwohl *et al.* teaches the treatment of all samples with proteinase K; denaturation of all proteins in said samples by boiling in 5% sodium dodecylsulfate; protein precipitation in methanol; resolublization of the precipitated proteins in buffer containing guanidine thiocyanate; and, finally, adsorption of the protein onto plastic plates for ELISA analysis. In contrast, claim 1 discloses no proteinase K digestion; proteins in the test set are denatured with guanidine thiocyanate; the test set and the control set are assayed for the presence of PrP; and the results of the test set and the control set are compared. And while claim 5 discloses proteinase K use, the newly added claim 20 clarifies proteinase K use by disclosing that only a subset of samples are to be treated with proteinase K.

Second, the method taught by Grathwohl *et al.* is based on the proteinase K resistance of PrP^{sc}. PrP^{sc} is highly aggregated and is thus resistant to proteolysis; the normal, monomeric, constitutively-expressed form of PrP (PrP^{c}) is, however, quite susceptible to proteolysis. This protease resistance/susceptibility dichotomy is used by Grathwohl *et al.* to differentiate between samples containing PrP^{sc} and those that contain only PrP^{c}. In contrast, claim 20 specifically discloses that the proteinase K digestion disclosed in claim 5 is to be used only on a subset of sample aliquots; and claims 1, 20 and 21 disclose that guanidine thiocyanate denaturation creates a differential in antibody reactivity between PrP^{sc} and PrP^{c} that is exploited to objectively detect the presence of PrP^{sc} without having to resort to proteinase K digestion. As disclosed in the newly added claim 20, a relative signal increase following guanidine thiocyanate denaturation is objective proof of the presence of PrP^{sc}.

Third, while Grathwohl *et al.* and the rejected claims both teach the use of guanidine thiocyanate, the shared reagent is used for different purposes each case. Grathwohl *et al.* teaches the use of guanidine thiocyanate to resolublize a mixture of proteins, which may or may not

include PrP^{sc}, after precipitation in methanol. In contrast, claim 1 discloses that guanidine thiocyanate or a functional equivalent thereof is used in a PrP specific fashion to create a differential in antibody reactivity between PrP^{c} and PrP^{sc}. Antibody reactivity towards PrP^{sc} is increased relative to PrP^{c} because denaturation in guanidine thiocyanate exposes antibody binding sites that are exposed on PrP^{c} but are hidden on PrP^{sc}.

Fourth, the primary antibodies disclosed in claims 11-13 are distinct form the primary antibody used by Grathwohl *et al.* For example, claim 11 discloses that the antibody used to detect PrP is directed "against the proteinase K resistant part" of PrP^{sc}. The antibodies are designed such that their ability to react with aggregated PrP^{sc} is limited, whereas they can fully react with PrP^{sc} when it has been denatured with guanidine thiocyanate or a functional equivalent thereof. By using the strategies disclosed in claims 11-13, the designer of the antibodies purposely created the guanidine thiocyanate antibody reactivity effect that is disclosed in claims 1, 20, and 21.

Fifth, claim 1 is specifically directed towards "reducing the risk of scoring a false-positive test result." As discussed in the specification, the consequences of scoring a false-positive can be quite serious. See *WO 00/48003* p. 16, lines 6-29. Claim 1 accomplishes "reducing the risk of scoring a false-positive test result" in part by dictating the preparation and analysis of controls. In brief, when an assay is prepared, parallel analyses are performed in which test results are compared with or without the effects of guanidine thiocyanate denaturation. Accordingly, a relative increase in antibody reactivity for a given sample following guanidine thiocyanate denaturation is objective proof of the presence of PrP^{sc}. The use of objective controls acts as an internal check on the validity of the test, and results in a reduced risk of scoring a false positive test result. In contrast, Grathwohl *et al.* does teach the collection of controls. The assay taught by Grathwohl *et al.* depends on complete digestion of PrP^{c} by proteinase K. If PrP^{c} is completely eliminated by proteinase K then any PrP signal detected by Grathwohl *et al.* can be said to be PrP^{sc}. However, under Grathwohl *et al.* there is no independent means of tracking the completeness of proteinase K digestion because they do not advocate the collection of controls before and after proteinase K digestion. The risk of scoring a false-positive test result with the method of Grathwohl *et al.* is therefore unacceptably high.

In conclusion, Grathwohl *et al.* does not anticipate claim 1 or the dependent claims that follow thereon for at least five reasons, thus rendering the claimed method nonobvious. 1) Grathwohl *et al.* and the rejected claims teach different methods of sample preparation; 2) the method taught by Grathwohl *et al.* depends on proteinase K digestion of all samples, whereas claims 1, 5, 20, and 21 disclose the use of guanidine thiocyanate to discriminate between forms of PrP and claims 20 and 21 disclose that the use of proteinase K is optional; 3) while Grathwohl *et al.* and claim 1 both disclose the use of guanidine thiocyanate, the reagent is used for different purposes in each case; 4) the primary antibody design disclosed in claims 11-13 is specifically directed towards detecting epitopes within the protease resistant core of the protein and is thus more specific for PrP^{sc}; and 5) claim 1 specifically reduces the risk of scoring a false-positive test-result by dictating the collection of controls, whereas Grathwohl *et al.* increases the risk of scoring a false-positive by not advocating the collection of controls. Reconsideration and withdrawal of these rejections is respectfully requested.

Rejections under 35 U.S.C. § 103(a):

Claim 18 stands rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Bell *et al.* (*Neuropathology and Applied Neurobiology*, 23(1):26-35, 1997). Claims 6, 7, and 18 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Grathwohl *et al.* Claim 18 has been canceled without prejudice or disclaimer, thus obviating the need to respond to that aspect of the rejection.

Rejections under Grathwohl *et al.*

In order to establish a prima facie case of obviousness under 35 USC § 103 all claim limitations must be taught or suggested by the reference. MPEP § 2143.03. Claims 6 and 7, which depend on claim 1, would not be obvious over Grathwohl *et al.* to one of ordinary skill in the art because the reference cannot reproduce the method disclosed in claim 1 or the claims dependent thereon for at least three reasons.

First, the method taught by Grathwohl *et al.* is based on the proteinase K resistance of PrP^{sc}. PrP^{sc} is highly aggregated and is thus resistant to proteolysis; the normal, monomeric, constitutively-expressed form of PrP (PrP^{c}) is, however, quite susceptible to proteolysis. This

protease resistance/susceptibility dichotomy is used by Grathwohl *et al.* to differentiate between samples containing PrP^{sc} and those that contain only PrP^{c}. In contrast, claim 1 discloses that samples are used to prepare a test set and a control set of subsamples. The test set is then denatured in guanidine thiocyanate while the control set is left untreated. Claim 1 further discloses that guanidine thiocyanate denaturation increases antibody reactivity towards PrP^{sc} while antibody reactivity towards PrP^{c} is unchanged or reduced. By comparing the antibody reactivity of subjects in the test set to the corresponding subjects in the control set, one can easily distinguish between samples obtained from healthy or diseased tissue. Furthermore, claim 20 specifically discloses that only a subset of samples are to be treated with protease.

Second, because the method taught by Grathwohl *et al.* depends on the ability of proteinase K digestion to remove all traces of PrP^{c}, the method of Grathwohl *et al.* would lead to an increased risk of scoring a false positive test result. Grathwohl *et al.* could mitigate this eventuality if they advocated collection and comparison of samples before and after proteinase K digestion, but they do not. The collection of control samples is important because the consequences of a false positive can be great. For example, if this test were used to screen slaughtered animals for transmissible spongiform encephalopathies, a false positive test would not only cause the affected production line to shut down needlessly, but it could also mandate that the animal's entire herd to be destroyed unnecessarily, and the affected nation's agricultural products could be embargoed. *WO 00/48003* p. 16, lines 6-29. Claim 1 is directed at reducing the risk of "scoring a false-positive test result" by dictating that assays be performed in parallel with one-half comprising a test group and the other half comprising a control group. By comparing the guanidine thiocyanate denatured set to the undenatured set, claim 1 provides for an objective set of criteria for judging the success of the test. That is, a relative increase in antibody reactivity following guanidine thiocyanate treatment is objective proof of the presence of PrP^{sc}. Because Grathwohl *et al.* does not teach the use of controls to aid in distinguishing between samples from healthy and diseased animals, as required by claim 1, their method would lead to greatly increased risk of scoring a false positive test result.

Third, while Grathwohl *et al.* and claim 1 both disclose the use of guanidine thiocyanate the manner and use of the reagent is unique in each. In the case of Grathwohl *et al.*, a buffer

containing guanidine thiocyanate is used to resolublize a mix of proteins after precipitation in methanol prior to adsorption onto microtiter plates for ELISA analysis. In contrast, claim 1 discloses the use of guanidine thiocyanate or a functional equivalent thereof in a PrP-specific fashion after the protein has been immobilized to a solid phase to create a differential in antibody reactivity between treated and untreated samples. If guanidine thiocyanate were used in the instant case as it is as taught by Grathwohl *et al.*, then the effect that is disclosed in claim 1 that allows one to readily differentiate between PrP^{sc} and PrP^{c} containing samples would be lost.

For at least the three foregoing reasons claim 1 would not be obvious over Grathwohl *et al.* to one of ordinary skill and their method cannot be combined with bovine or ovine samples to recreate claims 6 and 7. Claims 6 and 7 should therefore be seen as nonobvious under Grathwohl *et al.* because, *inter alia*, claim 1 is nonobvious. "If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious." MPEP § 2143.03.

Reconsideration and withdrawal of the rejections under Grathwohl *et al.* is respectfully requested.

Rejections under 35 USC § 112, second paragraph:

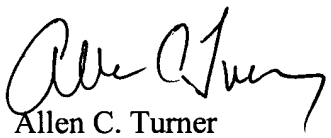
Claims 10, 13, 14, and 19 stand rejected under 35 USC § 112, second paragraph as assertedly being indefinite. Claim 19 has been canceled thus obviating the need to respond to the rejection. The word "derived" has been eliminated from claims 10 and 13 in accordance with the Examiner's suggestion from the Final Office Action of May 12, 2005. The word "derived" in claim 10 has been deleted. In claim 13, the phrase "a peptide derived" has been deleted and replaced with the phrase "an epitope." Claim 14 has been amended to make the wording agree with claim 13; the phrase "peptide is" has been replaced with "epitope has a sequence." Applicants believe that "epitope" is a perhaps more appropriate term because it is defined as a site on an antigen that is recognized by an antibody. Reconsideration and withdrawal of these rejections is respectfully requested.

Conclusion

In view of the amendments and remarks presented herein, the applicants submit that the

claims define patentable subject matter and a notice of allowance is requested. Should questions exist after consideration of the foregoing, the Office is kindly requested to contact the applicants' attorney at the address or telephone number provided.

Respectfully submitted,



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